

| | | |
|--|----|--|
| (51) International Patent Classification 5 : <div style="text-align: center; font-weight: bold; margin-top: 10px;">A61L 9/04</div> | A1 | (11) International Publication Number: WO 93/00115 (43) International Publication Date: 7 January 1993 (07.01.93) |
| (21) International Application Number: PCT/US92/05452 (22) International Filing Date: 26 June 1992 (26.06.92) (30) Priority data: <div style="display: flex; justify-content: space-between; margin-top: 10px;"> 722,704 28 June 1991 (28.06.91) US </div> (71)(72) Applicant and Inventor: FISCHER-GHODSIAN, Fariba [US/US]; 2122 Century Park Lane, Suite 104, Los Angeles, CA 90067 (US). (74) Agents: HENRY, Janis, C. et al.; Poms, Smith, Lande & Rose, 2121 Avenue of the Stars, Suite 1400, Los Angeles, CA 90067 (US). | | (81) Designated States: CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> |
| (54) Title: DEVICE FOR CONTROLLED RELEASE OF VAPOROUS MEDICATIONS AND INSECT-REPELLENTS | | |
| | | |
| (57) Abstract <p>A controlled release device useful for the release of vapors or liquids to the surrounding of the user is described. The device (30) is a multilayered laminate consisting of a reservoir layer (32) which incorporates an active compound, such as a nasally delivered therapeutic medication or insect repellent, an impermeable membrane layer (36) adjacent the reservoir layer and a diffusion rate limiting membrane layer (34) adjacent the reservoir layer. The device preferably includes an adhesive layer (38) for adhering the device to skin or a surface and an ornamental decorative layer.</p> | | |

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | |
|----|--------------------------|----|---------------------------------------|----|--------------------------|
| AT | Austria | FI | Finland | ML | Mali |
| AU | Australia | FR | France | MN | Mongolia |
| BB | Barbados | GA | Gabon | MR | Mauritania |
| BE | Belgium | GB | United Kingdom | MW | Malawi |
| BF | Burkina Faso | GN | Guinea | NL | Netherlands |
| BG | Bulgaria | GR | Greece | NO | Norway |
| BJ | Benin | HU | Hungary | PL | Poland |
| BR | Brazil | IE | Ireland | RO | Romania |
| CA | Canada | IT | Italy | RU | Russian Federation |
| CF | Central African Republic | JP | Japan | SD | Sudan |
| CG | Congo | KP | Democratic People's Republic of Korea | SE | Sweden |
| CH | Switzerland | KR | Republic of Korea | SN | Senegal |
| CI | Côte d'Ivoire | LI | Liechtenstein | SU | Soviet Union |
| CM | Cameroon | LK | Sri Lanka | TD | Chad |
| CS | Czechoslovakia | LU | Luxembourg | TG | Togo |
| DE | Germany | MC | Monaco | US | United States of America |
| DK | Denmark | MG | Madagascar | | |
| ES | Spain | | | | |

**DEVICE FOR CONTROLLED RELEASE OF VAPOROUS
MEDICATIONS AND INSECT-REPELLENTS**

BACKGROUND OF THE INVENTION

This application is a continuation-in-part of copending application Serial No. 07/537,438 which was filed on June 13, 1990.

1. Field of the Invention

The present invention relates in general to controlled release devices which are useful for dispensing an active compound from an article to the environment surrounding the article. More particularly, the present invention is directed to vapor emitting devices which form a laminate and provide a continuous release of a vapor at a substantially constant release rate. The present invention also relates to liquid release devices which form a laminate and provide a continuous release of a liquid or a solid dissolved in a liquid at a substantially constant release rate. The invention also relates to methods of preparing the laminates.

2. Description of Related Art

Various devices and compositions designed to release vapors or liquids from a compound or combinations of compounds have been in wide use over the years. For example, air freshener devices which continuously release an aroma into the environment surrounding the device exist in several varied configurations. Such devices range from a simple cardboard or paper structure saturated with air freshener for use in a confined area to elaborate and decorative air fresheners with more complicated aroma release mechanisms.

Also available are air fresheners with a "designer" appearance which adhere to surfaces and contain an air freshener compound within the device. The aromatic air freshener vapors are then released into the surrounding

environment for a sustained length of time. The design and construction of these air fresheners is such that they release the vapors from the air freshener compounds at a rapid rate when the device is first put into service. As a result, the release rate diminishes significantly after a relatively short period of time. This produces a vapor release time profile where a relatively large amount of the total available air freshener is released in the initial part of the release period and only a small amount released thereafter. In many cases the aroma is too heavy during the initial part of the intended release period and too little or negligible at the end of the release period. Ideally, the release of the air freshener should be constant during the life of the device.

Other similar vapor releasing devices are perfume patches or pads which provide a temporary short term pleasant odor to the environment in the immediate vicinity of the patch or pad. The most prevalent use for these devices is to advertise perfumes to the public dispensing scent samples in the form of perfume patches or pads. The samples customarily consist of the perfume absorbed on a paper type support. They provide a short term release of the perfume's vapors after which the patch or pad is discarded.

United States Patent No. 4,880,690 describes a perfume patch which is a laminate of polyurethane in combination with other layers including an impermeable backing and adhesive layer. The patch incorporates a perfume in the polyurethane layer and is intended to be adhered to the user's skin in areas such as behind the ear. Additionally, the patch may have an added pigment or decorative design on the polyurethane layer which lends some artistic appeal to the laminate.

The above described perfume pads and perfume patches have the same disadvantages as the air freshener release devices. The perfumes have a rapid rate of

release during the initial phase of their life and a significantly reduced rate of release in the later stages. In order to prolong the use time of the patches and increase the release rate later in the life of the pad or patch, it is necessary to increase the perfume loading in the device. Increasing the loading of perfume in the device causes an increase in the initial release rate which in turn may cause an unpleasantly high amount of perfume vapor in the environment.

Controlled release devices also find application for the sustained release of breath fresheners. The use of water soluble mints and other suitable agents for controlling breath odor in devices designed to be contained or adhered to portions of the mouth are known in the art. These sustained release devices normally incorporate the active breath freshener in a device which slowly dissolves over a 1 to 4 hour period and releases the freshener as the dissolution proceeds. Breath fresheners which release active compounds in this manner have a relatively high surface area during the initial portion of the release period resulting in a high dose of the active compound. As dissolution of the article continues the surface area substantially decreases and the dose of the breath freshener necessarily decreases as well. This results in a less than desirable amount of freshener in the mouth.

Controlled release devices are used extensively in the pharmaceutical industry to provide therapeutic and diagnostic compounds to patients over periods of time ranging from minutes to days. In particular, skin patches have been used successfully in administering medications transdermally for several hours at a time with just one patch application. In particular, a patch described in United States Patent No. 4,031,894 for delivering the sea sickness medication, scopolamine, is a five layer laminate designed to be attached to the skin behind the user's ear and deliver the drug through

the patch's adhesive layer and into the user's circulatory system.

5 The utility of these skin patches, however, is limited to delivering therapeutic agents or other active compounds through the user's skin.. The effectiveness of these skin delivery systems depends significantly upon the skin mass transport properties of the therapeutic agent and can vary from user to user. Additionally, these therapeutic agents frequently require a carrier or solvent to enhance their transport properties.

10 In addition to the above mentioned applications release devices have been used to release insect control and insect repellents on animals for decades. For example, flea and tick repellent and insecticides are incorporated in pet collars and then released onto the pet while the pet is wearing the collar to help control fleas and ticks which come into contact with the animal. Such collars are particularly adaptable for pets because it is difficult to apply insect repellents and insecticides to animal skin and fur on a regular basis.

20 Additionally, people have used insect repellents directly on the skin for over 30 years. Moreover, the use of insect repellents has increased dramatically in recent years in conjunction with the heightened concern associated with Lyme disease and the fear that mosquitos and other insects may contribute to the spread of AIDS. Known methods for delivering insect repellents in a manner which is safe and efficacious tend to be dangerous, short-acting and inconvenient. Recent clinical observations have shown that DEET, a leading topically applied insect repellent can cause severe central nervous system toxicity and even death from skin penetration. This is a particularly significant problem for children who have larger body surface area-to-mass ratios and higher skin permeability. Additionally, children tend to lick their fingers and hands, which can cause them to ingest the insect repellents.

Another problem associated with topically applying insect repellents directly to the skin is that they are effective for only short periods of time. Because the insect repellent is removed by skin absorption, evaporation, perspiration, and through participation in water activities, it must be reapplied at frequent intervals. The requirement for frequent reapplications results in a continual threat of systemic toxicity to the user.

There is a need to provide a controlled release device which will continuously release vapor into the environment surrounding the user at a controlled, and substantially constant rate over the intended life of the controlled release article.

There is additionally a need to provide controlled release devices which safely and effectively deliver active compounds and therapeutic agents without applying the active compound directly to the skin or depending upon the mass transport properties of the active compound through the skin.

There is also a need to provide a liquid releasing device which will continuously release liquids into a suitable environment at a controlled and substantially constant rate over the intended life of the release article.

SUMMARY OF THE INVENTION

It is a principal objective of the present invention to provide a controlled release device which delivers an active compound from the device at a substantially constant rate.

It is an additional object of the present invention to provide a controlled release device which adheres to a surface for the duration of the release period.

It is another object of the present invention to provide a controlled release device which delivers active compounds or therapeutic agents without applying

the active compound or therapeutic agent directly to the skin.

5 It is a further object of the present invention to provide a controlled release device which incorporates a decorative design for its additional use as an ornamental object.

10 It is a further additional object of the present invention to provide a controlled release device which will controllably deliver vapors or liquids for a period of from one to seventy-two hours.

15 The present invention accomplishes the above described objectives by providing a controlled release device in the form of a laminate which consists of at least one layer of a diffusion rate limiting membrane placed adjacent a second layer which incorporates the active compound. The controlled release devices of the present invention may be decoratively embellished with ornamental designs without interfering with the release properties. Additionally, the laminate design provides 20 a means of maintaining an adhesive layer which allows the device to adhere to a variety of surfaces for the duration of its active life. The controlled release device of the present invention may be configured in any of a variety of shapes and sizes depending upon the active compound of choice, the environment of its 25 intended use, and the duration of its intended use.

The controlled release devices of the present invention are multilayer laminates with an active compound incorporated in a reservoir layer. The active 30 compound may be any of a number of useful vapor emitting compounds such as perfumes, various fragrances, air fresheners, insecticides, and insect repellents. The active compound can also be therapeutic agents such as vapor emitting compounds, and those which are typically 35 delivered by aerosol or spray inhalation. These therapeutic agents include antihistamines, bronchodilators, decongestants, anti-tussives,

mucolytics, steroids, anti-virals, hormones and peptides.

5 Additionally, the active compound may be intended for use in its liquid or dissolved form, e.g. breath fresheners. The laminates of the present invention are constructed such that the active compound diffuses from the reservoir layer into a diffusion rate limiting membrane layer where the vapor or liquid is released into the surrounding environment at a substantially
10 constant rate over the intended life of the device. If desired, for applications in which the controlled delivery device is utilized in visible areas, an ornamental or decorative layer may be incorporated for added appeal.

15 In accordance with the present invention, the controlled release device may be configured with an impermeable backing which prevents contact of active compound with the skin and an adhesive layer which allows the device to adhere to wall surfaces, skin,
20 clothing, mucosa tissue, and other items without affecting the release properties. Additionally, the adhesive-surface bond remains intact during its period of use without interference from the active compound.

25 The controlled release devices of the present invention may be formed into a variety of three dimensional structures ranging in thickness from 200 microns to several millimeters and with surface areas of from about 1 cm² to several 100 cm². In this manner, the available surface area and the thickness of the
30 reservoir layer may be varied to meet the needs of the application. For most applications, the device configuration will be sized for a 12 to 24 hour release period for a convenient once a day administration. Shorter and longer release periods are also contemplated as being
35 within the scope of the present invention.

Further objects of the controlled delivery devices of the present invention, as well as a better

understanding thereof, will become apparent from a consideration of the following detailed explanation of the preferred exemplary embodiments thereof.

5

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is an illustration of a controlled release device which forms a laminate comprising a reservoir and a diffusion rate control membrane, and an impermeable backing.

10

FIG. 2 is an illustration of a controlled release device of FIG. 1 which additionally contains a decorative layer.

15

FIG. 3 is an illustration of a controlled release device which has an adhesive layer, an impermeable backing layer, a reservoir layer, and a diffusion rate limiting membrane.

20

FIG. 4. is an illustration of the controlled release device of FIG. 3 which additionally contains a decorative layer.

25

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

30

The present invention is a controlled release device in the form of a laminate which may be utilized in any of a number of applications in which it is desirable to release vapors or liquid from an active compound into the environment surrounding the compound. The controlled release device of the present invention provides a substantially constant controlled rate of release of the vapor or liquid from the device. This is accomplished by incorporating a diffusion rate limiting membrane layer into the laminate which controls the rate at which the active compound diffuses to the surface of the device and vaporizes or dissolves into the environment surrounding the device.

35

An exemplary controlled release device produced in accordance with the teachings of the present invention is shown in FIG. 1. The device 10 as shown is a cross-

sectional view of a laminate that consists of three layers: a reservoir layer 12 which incorporates an active compound or compounds, a diffusion rate limiting membrane layer 14 adjacent to the reservoir layer, and
5 an impermeable backing layer 16.

In accordance with the present invention the reservoir layer 12 is a porous polymer which is physically and chemically compatible with the active compound or compounds of choice. Suitable polymers include any of
10 a number of foams having cell sizes with a porosity range of from about 0.1 to about 0.8. Appropriate foams are urethane foams, styrene foams, polyvinylchloride foams, polypropylene foams, polyethylene foams, silicone foams and rubber foams. Additionally, polymers which
15 form porous morphologies such as the polypropylene ACCUREL® manufactured by Armac Co., polyethylene, acrylates, and polyurethanes may be utilized to form the reservoir layer.

The active compound of choice may be incorporated
20 into the reservoir layer polymer by conventional methods known in the art for incorporating polymeric additives. These methods include preforming the polymer foam or the porous polymer or hydrogel and immersing the polymer in the active compound or a solution of active compound for
25 a length of time sufficient to saturate the pores of the polymer. Active compounds may be incorporated with loading levels from about 10% to about 80% by weight of the reservoir.

Alternatively, the active compound of choice may be
30 incorporated in the system utilized to produce the polymer itself, e.g. the monomer or monomers forming the polymer may be dissolved in the active compound and the monomers subsequently polymerized by conventional means to form the polymer. In this manner the vapor emitting
35 compound and the polymer form either a single phase system much like a plasticized polymer, or the active compound and the polymer form a two phase system in

which particulates of the compound are dispersed throughout the polymer.

Another embodiment of the reservoir layer of the laminate is in the form of a gelled mixture of a polymer and a liquid. In the case of when the active compound of choice is an oil soluble compound it may be incorporated into a gelled mixture of an oil and polymer. And in the case of when the vapor emitting compound of choice is a water soluble compound it may be incorporated into a gelled mixture of water and a polymer. In applications in which the vapor emitting compound is required at high concentrations within the reservoir layer polymer, the active compound itself can form the liquid portion of the gel without the added oil and water.

As in the case of all polymers which are suitable for use in the reservoir layer of this invention, both the liquid and the polymer which form the gel must be physically and chemically compatible with the active compound. Any gelled mixtures of oil and polymer and gelled mixtures of water and polymer known in the art and suitably compatible and non toxic may be used. Among these gelled mixtures are oil and polyisobutylene, oil and isoprene, oil and silicone, water and polyvinylpyrrolidone, water and hydroxyethylmethacrylate, and combinations including hydroxypropyl cellulose. In addition to diluents and gelling agents, reservoir 12 may include other materials such as stabilizers.

Referring again to FIG. 1, the diffusion rate limiting membrane layer 14 is a thin membrane of from about 10 microns to about 100 microns. It is a microporous polymer which can be selected from any one of the polymers known in the art which is available as a thin microporous membrane with pore sizes ranging from 0.02 microns to about 0.6 microns. Alternatively, it can be a non-porous polymeric membrane which transports the

active compound through dissolution in the polymer. Suitable polymers include ethylene vinyl-acetate, polyethylene, polypropylene, polyvinylchloride, cellulose acetate, cellulose nitrate, polyacrylonitrile, and polytetrafluoroethylene.

The diffusion rate limiting membrane 14 is the layer of the laminate that controls the rate at which the vapor or liquid is emitted or released from the active compound which is incorporated into the device. The release rate is a function of the thickness, the porosity, the tortuosity, the concentration gradient of the active compound across the membrane, and the diffusion coefficient of the compound. The active compound diffuses into the micropores of the diffusion rate limiting membrane layer and then is released at a substantially constant rate over the life of the device. This contrasts with the release mechanism of release devices lacking the rate limiting membrane which release very quickly early in their life and release at a significantly slowed rate thereafter.

Impermeable backing layer 16 is a material which does not allow the diffusion of gases and liquids. The backing provides a barrier to the diffusion of the active compound past the edge of the reservoir layer adjacent the impermeable backing layer.

Preferably the vapor and liquid impermeable backing 16 is itself a laminate and consists of a metal foil lined polymer. The polymer may be any polymer which is compatible with the active compound. Suitable candidate polymers include polyethylene terephthalate, high density polyethylene, low density polyethylene, polypropylene, and polyvinylchloride, and polyethylene/aluminized polyester/ethylene vinyl acetate.

For controlled release devices in which the reservoir layer 12 does not provide the necessary "tacky" surface for adhering to the impermeable backing

layer 16 and the diffusion rate limiting layer 14, it is desirable to provide a clip or other component for securing the layers of the device together. This component may be a miniature clip, such as the clip shown in phantom at 18 in FIG. 1 which is secured over each face of the device, or a small amount of an adhesive, such as an epoxy, applied to the edges. Alternatively, the laminate layer edges may be secured by heat or solvent sealing techniques. In addition to providing a support system for the layers of the device, the clip 18 or other components prevent the loss of the active component from the edges of the reservoir.

Active compounds which are contemplated within the scope of the present invention include vapor emitting compounds such as perfumes or other fragrances. More particularly, suitable vapor emitting compounds are naturally occurring essential oils, air fresheners, insecticides, therapeutic agents and insect repellents. Suitable therapeutic agents include over the counter and prescription drugs which can be delivered by aerosol or spray inhalation and which have vapor pressures sufficiently high to have a therapeutic effect. Particularly suitable therapeutic agents are antihistamines, bronchodilators, decongestants, anti-tussives, mucolytics, steroids, antivirals, peptides and hormones. When the reservoir layer of the laminate incorporates one or more of a vapor emitting compound, the compound diffuses to the edge of the reservoir layer and comes into contact with the diffusion rate limiting membrane layer. The vapor emitting compound fills the pores as it diffuses and then is controllably vaporized at a substantially constant rate into the environment surrounding the device.

Additional active compounds also within the scope of the present invention are liquids or dissolved solids such as breath fresheners which are intended to be released into a liquid environment. When incorporated

into the reservoir layer of the laminate with a diffusion rate control membrane layer, the liquid diffuses into the micropores of the membrane layer and then becomes solubilized by the liquid environment surrounding the device. When the active compound is a solid which is dissolved in a liquid the diffusions of the solid may be enhanced by prefilling the micropores with the appropriate liquid. In the case of a breath freshener this liquid is water.

The overall size and thickness of the controlled release devices of the present invention depends upon the intended use of the device, the nature of the active compound, and the length of time desired for the device to be in use. In some instances the device may be as thin as 0.02 cm with an area of 4 or 5 cm². For other applications requiring longer release times with a diffusing vapor emitting compound, the total laminate thickness may be several millimeters thick.

The controlled release device of FIG. 1 is useful in applications such as releasing insecticide vapors. In particular, pendants intended for use by pet owners as flea and or tick controlling devices may be made from laminates formed by the vapor emitting device. Such flea and tick control devices may be suspended from the animals personal collar and worn by the animal for up to one week and then discarded. The reservoir layer of the vapor emitting devices intended for use as flea and tick control device must be several millimeters thick and 5 to 10 cm² in area with insecticide contents of from 20% to 60% to provide a sustained and constant supply of insecticide for one week.

FIG. 2 illustrates another embodiment of the present invention. FIG. 2 illustrates a laminate that consists of four layers: a reservoir layer 22, a diffusion rate limiting membrane layer 24, an impermeable backing layer 26, and a decorative layer 28. The reservoir layer 22, rate limiting membrane layer 24,

and impermeable backing layer 26 have properties and characteristics as described for FIG. 1. Decorative layer 28 is preferably a thin permeable polymeric material which will readily transmit the active compound and at the same time provide an ornamental quality to the controlled release device. Useful applications of this decorative device include ornamental "jewelry" type pendants which incorporate a perfume or naturally occurring essential oil fragrance. This device will emit a perfume or fragrance for a period of from 6 hours to 24 hours. Such pendants can be worn for a day and then disposed of after a one time use. The decorative controlled release devices for emitting vapors used in this manner find a particularly advantageous utility by those persons who are allergic to perfumes or have otherwise incompatible skin types for wearing perfumes or fragrances.

Another useful application is a decorative device which incorporates insect repellent material. This device will emit an insect repellent for a period of from about 6 hours to 24 hours. Typical uses for such devices for delivering insect repellents in a controlled manner are in the form of pendants hanging from pet collars or in the form of the collars themselves for the control of ticks and fleas. Pendants or devices located in living areas which are intended to repel insects from the vicinity are also suitable applications for controlled release devices of the present invention.

Also within the scope of the invention as shown in FIG. 2 are decorative controlled release devices used for emitting air fresheners. Such vapor emitting devices may be suspended in an enclosed area where they emit the air freshener at a substantially constant rate over a period of several hours and up to one day in duration.

FIG. 3 depicts another embodiment of the present invention, generally designated laminate 30. This pre-

ferred embodiment is suitable for adhering to a surface while emitting vapors, liquids, or dissolved solids of choice. In accordance with the teachings of the present invention the features of this embodiment include a
5 diffusion rate limiting membrane 34, a reservoir layer 32, adjacent the diffusion rate limiting membrane layer, a vapor and liquid impermeable backing layer 36 adjacent the diffusion rate limiting membrane layer, and a
10 pressure sensitive contact adhesive layer 38 adjacent the impermeable backing layer.

The diffusion rate limiting membrane 34 has the properties and characteristics of the diffusion rate limiting membrane discussed above. The presence of the membrane is necessary for the effective control of the
15 release rate of the active compound from the device. The membrane, as discussed above, is responsible for the substantially constant rate of release of the active compound over the life of the device.

Adjacent the diffusion rate limiting membrane layer
20 34 is the reservoir layer 32 incorporating the active compound of choice. Reservoir layer 32 may consist of any of the polymeric forms discussed above in the description of FIG. 1. Adjacent the reservoir layer 32 is a vapor and liquid impermeable backing 36. In
25 addition to being a barrier to contact of the active compound with skin, the impermeable backing layer 36 further provides a means to prevent the active compound from interfering with the function of the adhesive as will be discussed below.

30 Adjacent the vapor and liquid impermeable backing 36 is an adhesive layer 38. The adhesive may be any pressure sensitive contact adhesive suitable for applying to a surface such as the acrylate contact adhesives. When the controlled release device is
35 intended to be used on the skin or any tissue area of a person the contact adhesive must additionally be non-toxic, biocompatible, and hypoallergenic. In particular

the biocompatible adhesive may be suitable acrylates, and hydroxypropyl cellulose, medical grade silicone adhesives and their derivatives.

5 The adhesive is applied to the impermeable backing layer 36 of the laminate. The backing material prevents the diffusing active compound from diffusing into the adhesive layer 38 and diminishing the effectiveness of the adhesive by solubilizing it or destroying the surface-adhesive bond. It is also undesirable for the active compound to diffuse in the direction of the adhesive since a) it may be irritating to the skin or toxic to the body upon absorption and b) the target release point is the environment bound by the diffusion rate limiting membrane 34.

15 The attendant advantages of the embodiment of the present invention as illustrated in FIG. 3 is the ability of the controlled release device to be conveniently adhered to any surface which will accept the pressure sensitive contact adhesive layer. For example, it is contemplated within the scope of the invention to form a laminate as depicted in FIG. 3 with a reservoir layer 32 which incorporates an air freshener emitting compound and having dimensions of from about 5 cm² to about 500 cm² and about 0.2 mm thick. The device may be adhered to the surface of the interior of an automobile or and the wall surface of an interior room. It will effectively release the air freshener over a desired time period at a substantially constant rate.

25 Also contemplated within the scope of the invention as shown in the embodiment of FIG. 3 are controlled release devices for the release of breath fresheners. The reservoir layer 32 incorporates from 20% to 60% of a water soluble mint or other liquid or solid which is suitable and safe for use as a breath freshener. The device may be adhered to a tooth, the buccal cavity, gum, or palate of a user. Once secured in the user's mouth, the breath freshener is released at a constant

rate over a period of time ranging from less than an hour to several hours.

5 Likewise the self-adhering qualities of the laminate of FIG. 3 make these devices suitable for releasing insecticides from a controlled release device adhered to a pet collar. In this application insecticides useful for controlling fleas and ticks on
10 pets are incorporated in the reservoir layer 32. The controlled release laminate as shown in 32 is then adhered to a pet's collar by applying the adhesive layer 38 to the outer surface of the collar. This application has the advantage of providing a uniform release rate for the insecticide rather than allowing the pet to experience a high dose of insecticide during the initial
15 stages of the insecticide release. Pet owners can easily replace the controlled release device with minimum expense by removing it from the pet's collar and applying a new insecticide releasing device.

20 Another related application for the controlled release device illustrated in Fig. 3 is that of a device for releasing insect repellent. Commonly used insect repellents, such as N, N, diethyl-meta-toluamide (DEET) are conveniently incorporated in the reservoir layer 32 utilizing methods described above. The resulting
25 controlled release laminate device is adhered to a user's exposed skin area by applying the adhesive layer 38 directly to the skin. For complete protection a plurality of controlled release devices can be adhered to a plurality of exposed skin areas, such as arms,
30 legs, and the forehead. Generally, the controlled insect repellent devices are designed for a one time use in that they are worn for a period of hours and then removed and discarded.

35 Controlled release devices of the present invention which have the general configuration shown in Fig. 3 and incorporate insect repellents as described above, advantageously can be formulated to deliver doses of

insect repellent ranging from light to heavy. Thus, controlled insect repellent release devices can be tailored for use by adults and children. Additionally, because these insect repellents are delivered to a surrounding environment without applying the insect repellent directly to the skin, user's having skin or systemic sensitivities to the repellent can use them without fear of adverse reactions. Thus, these controlled insect repellent release devices eliminate potential health hazards associated with common insect repellent ointments, such as the risk of cancer and nervous system toxicity and they are particularly beneficial for children.

As mentioned above, controlled release devices having the embodiment illustrated in Fig. 3 are also suitable for applications in which therapeutic agents are incorporated in the reservoir layer 38. For example, a controlled release device which incorporates camphor in the reservoir layer 32 can be adhered above a user's upper lip by applying the adhesive layer 38 to the user's skin. Since camphor has a relatively high vapor pressure, it vaporizes and is released in a controlled manner into the nasal passage and to the respiratory airway.

Therapeutic agents having vapor pressures sufficiently high to provide a therapeutic dose to the lungs, respiratory airway or nasal vascular system while positioned in close proximity to the nasal passage have utility in the controlled release devices of the present invention. In particular, persons suffering from asthma or other allergic reactions or common cold and nasal congestion can wear controlled release devices at night or during indoor activities. These devices incorporate antihistamines, bronchodilators and decongestants and provide the beneficial effects of the therapeutic agent throughout the night or day. In addition, because medication is directly targeted to the nasal airway and

lungs, significantly lower doses are required and systemic absorption and side effects (such as hypertension) are minimized.

5 Controlled release devices of the present invention having the embodiment of Fig. 3 and incorporating a therapeutic agent for delivery through the nasal passage can be prepared using the techniques and materials described above for fabricating laminates. Typically the reservoir layer incorporates from 20 wt% to 90 wt%
10 therapeutic agent. The size and thickness of the laminate can vary, depending upon whether it is used on adults or children. However, the size generally conforms to that of an upper lip or about 0.5 cm x 2 to 3 cm.

15 A variation of the embodiment of the present invention illustrated in FIG. 3 is detailed in the laminate of FIG. 4. In accordance with FIG. 4 a decorative layer 50 is adjacent the diffusion rate limiting membrane layer 44. A reservoir layer 42 is
20 adjacent both the diffusion rate limiting, membrane layer 44, and an impermeable backing layer 46. An adhesive layer 48 is adjacent the impermeable backing layer 46. The diffusion rate limiting membrane 44, reservoir layer 42, impermeable backing layer 46, and
25 adhesive layer 48 have properties and characteristics as described for FIG. 3. The decorative layer 50 preferably is comprised of a thin highly porous material of polyester base which freely allows the released vapors to diffuse from one surface to the other surface
30 and into the surrounding environment.

A useful application of the laminate pictured in FIG. 4 is a perfume emitting device. The active compound is a vapor emitting perfume and is incorporated
35 into the reservoir layer according to methods known in the art as described above. Further and in accordance with the present invention the perfume emitting device may be decoratively worn by adhering the device to the

clothing or the skin of its user. By simply pressing the laminate to clothing or skin, the user has an attractive means to "wear" perfume. The diffusion rate limiting membrane used in combination with the reservoir layer which incorporates the perfume provides a means to effectively and continuously deliver a pleasing aroma at a substantially constant rate for a period of from 6 hours to 24 hours. Persons who prefer to wear perfume but are precluded from doing so because of allergies or skin chemistries are particularly suitable users for the perfume emitting device. Likewise, persons who are drawn to the long lasting scent of perfume on the body or the pleasing appearance of the decorative aspect or the variety afforded by the many different designs which may be available are also potential users.

Another useful application of the laminate pictured in FIG. 4 is an insect-repellent device. The active compound is a vapor emitting insect repellent and is incorporated into the reservoir layer according to methods described above. The insect repellent emitting device may be decoratively worn by simply pressing the laminate and adhering the device to the clothing or the skin of its user. The diffusion rate limiting membrane provides a means to effectively and continuously deliver a protecting odor at a substantially constant rate for a period of from 6 hours to 24 hours. Persons who want to use insect repellents, but do not like the greasy feeling on their skin, or are precluded from doing so because of skin allergies or skin absorption and systemic toxicity are particularly suitable users for the insect-repellent emitting device. Likewise, persons who are drawn to the long lasting effect of the insect repellent on the body or the pleasing appearance of the decorative aspect are also potential users.

The other useful application of the laminate pictured in FIG. 4 is a device that releases therapeutic medications. The active compound which is incorporated

in the reservoir layer is a vapor emitting medication such as camphor or a bronchodilator, against diseases such as common cold or asthma. The patient can use the device by simply pressing and adhering the laminate above the upper lips during sleep time or indoor activities. The diffusion rate limiting membrane used in combination with the reservoir layer which incorporates the medication provides a means to effectively and continuously deliver the medication to the nasal and respiratory airway at a substantially constant rate for a period of from 6 hours to 24 hours. Patients who do not want to take large doses of medication or want to minimize systemic side effects are particularly suitable users of this device. Likewise, the decorative aspect of the system and its different designs may provide means to encourage children to take the medication.

Also within the scope of the present invention are methods for using the controlled release devices of the present invention. For example, methods for controlling insects include the steps of providing a controlled release device having the form of a laminate. The laminate includes a diffusion rate limiting membrane layer and a reservoir layer adjacent the diffusion rate limiting membrane layer which also incorporates an insect repellent. The laminate further includes a vapor and liquid impermeable backing layer adjacent the reservoir layer and an adhesive layer adjacent the impermeable backing layer. The next step includes adhering the controlled release device to a surface such as a wall, window, or preferably to the skin of a person. After a period of several hours, up to about 24, the controlled release device is removed and a new one applied if desired.

Similar methods for delivery of therapeutic agents are also within the scope of the present invention. For example, by providing a controlled release device in the

form of a laminate having the same layers described above with a therapeutic agent such as camphor incorporated in the reservoir layer and adhering the laminate above the upper lip of a person, the therapeutic agent is delivered to the person's nasal passage and respiratory airway.

The following examples are illustrative of the various applications available to those who practice the teachings of the present invention. These examples are not intended to limit the invention in any manner.

Example 1

A perfume emitting device comprising the general laminate form shown in FIG. 4 is prepared using the following procedure and materials. An adhesive solution of a medical grade silicone adhesive is prepared by dissolving the silicone adhesive in isopropyl alcohol to a 5% by weight adhesive content. A peeling layer consisting of a standard form release paper is spread in a flat cast vehicle. The 5% solution of adhesive in isopropyl alcohol is then poured onto the peeling layer of standard release paper and the isopropyl alcohol is subsequently allowed to evaporate. The resulting adhesive layer is between 50 to 75 microns thick.

After the isopropyl alcohol is evaporated, a gas and liquid impermeable membrane layer consisting of an approximately 50 microns membrane of a medium low density polyethylene/aluminized polyester/ethylene vinyl acetate is placed on the adhesive layer. A polymer gel of perfume emitting compound and hydroxypropyl cellulose is then prepared by adding enough of a perfume to powdered hydroxypropyl cellulose to prepare a 50% by weight perfume-polymer gel. The hydroxypropyl cellulose is KLUCEL with a molecular weight of 1,000,000.

The polymer-perfume gel is then spread onto the impermeable membrane layer forming the reservoir layer of the laminate. A diffusion rate limiting membrane

consisting of a 40 microns thick ethylene vinyl-acetate available from Bertak was then placed adjacent the reservoir layer.

5 The laminate is topped with a self-adhering decorative layer prepared of porous polyester. For shipping and storage a second peeling layer prepared from any standard release paper which is impermeable to the perfume is placed over the decorative layer.

10 The final perfume emitting device prepared according to the method described above is a laminate of about 4 cm² and from 200 to 300 microns thick. The device is safely and conveniently used by peeling the release paper from each face of the laminate and pressing against the user's clothing or skin. In
15 accordance with the provisions of the present invention the laminate releases the pleasant aroma of the perfume at a substantially constant release rate for a period of 16 hours.

20

Example 2

An insect repellant emitting device comprising the general laminate form shown in FIG. 4 is prepared using the following procedure and materials. An adhesive solution of medical grade silicone adhesive layered on
25 a peeling layer is prepared according to the method described in the first paragraph of Example 1.

A gas and liquid impermeable membrane layer consisting of an approximately 50 micron thick membrane layer of a medium low density polyethylene/aluminized polyester/ethylene vinyl acetate is placed on the
30 adhesive layer. A polymer gel of insect repellant emitting compound and hydroxypropyl cellulose is then prepared by adding enough of an insect repellant to powdered hydroxypropyl cellulose to prepare a 50% by weight insect repellant-polymer gel. The hydroxypropyl
35 cellulose is KLUCEL with a molecular weight of 1,000,000.

5 The polymer-insect repellant gel is then spread onto the impermeable membrane layer forming the reservoir layer of the laminate. A diffusion rate limiting membrane consisting of a 40 micron thick ethylene vinyl-acetate available from Bertak is then placed adjacent the reservoir layer.

10 The laminate is topped with a self-adhering decorative layer prepared of porous polyester. For shipping and storage a second peeling layer prepared from any standard release paper which is impermeable to the insect-repellent is placed over the decorative layer.

15 The final insect repellant emitting device prepared according to the method described above is a laminate of about 4 cm² and from 200 to 300 microns thick. The device is safely and conveniently used by peeling the release paper from each face of the laminate and pressing against the user's clothing or skin. In accordance with the provisions of the present invention
20 the laminate releases the insect repellant without the potentially toxic or carcinogenic insect repellant contacting or absorbing through the user's skin.

Example 3

25 A breath freshener comprising the general laminate shown in FIG. 3 is prepared using the following procedure and materials. An adhesive consisting of a polysaccharide type mucoadhesive is spread on a peeling layer of standard form release paper to a thickness of
30 about 100 microns. A liquid impermeable membrane layer consisting of an approximate 100 microns membrane of aluminized polyethylene terephthalate is placed on the adhesive layer.

35 A polymer gel comprising about 60% liquid flavoring material, e.g. mint, in a gelled gelatin is prepared by incorporating the mint in the gelatin-water system before it gels and allowing it to gel. The mint-gelatin

gel is then spread onto the impermeable membrane layer forming the reservoir layer of the laminate and having a thickness of about 200 microns. A diffusion rate limiting membrane consisting of a 50 to 100 microns thick porous polytetrafluoroethylene film is then placed adjacent the reservoir layer. The resulting laminate is then cut into squares or circles of 1 to 2 cm² for use as sustained release breath fresheners. The breath fresheners prepared in accordance with this invention may be adhered to tissue or tooth surfaces in the users mouth and will controllably release the mint at a constant rate over several hours.

Example 4

A device useful for the sustained and controlled release of air fresheners comprising the general laminate form shown in FIG. 4 is prepared using the following procedure and materials. An acrylate adhesive is spread on a peeling layer of standard form release paper to a thickness of approximately 75 microns. A gas and liquid impermeable membrane layer consisting of an approximately 200 microns membrane of a medium low density polyethylene/aluminized polyester/ethylene vinyl acetate is placed on the adhesive layer. An air freshener is incorporated in a 400 microns thick layer of ACCUREL porous polypropylene having a 80% void volume by immersing the ACCUREL in the air freshener for three hours. Following the immersion step the ACCUREL is placed on the impermeable membrane layer which is followed by placing a diffusion rate limiting membrane of cellulose nitrate having a pore size of about 0.1 microns. The device is finished with a decorative covering of polyester which provides an added ornamental appeal.

The laminate of Example 3 is cut into sections of approximately 100 cm² and made available for adhering to the walls of kitchens, bathrooms or other environments

suitable for using an air freshener. The active compound of this laminate is made available to the environment in vapor form over several days at a constant rate.

5

Example 5

A device useful for the sustained and controlled release of a therapeutic agent, camphor, and having the general laminate form shown in Fig. 3 is prepared using the following procedure and materials. An adhesive solution of medical grade silicone adhesive layered on a peeling layer is prepared according to the method described in the first paragraph of Example 1.

10 A gas and liquid impermeable membrane layer consisting of an approximately 50 micron thick membrane layer of a medium low density polyethylene/aluminized polyester/ethylene vinyl acetate is placed on the adhesive layer. A polymer gel of camphor, water, and hydroxypropyl cellulose is then prepared by combining the three materials until a stiff gel results with the camphor comprising about 75 wt% of the gel

15 The polymer-camphor gel is then spread onto the impermeable membrane layer forming the reservoir layer of the laminate. A diffusion rate limiting membrane consisting of a 40 micron thick ethylene vinyl-acetate available from Bertak is then placed adjacent the reservoir layer.

25 Optionally, part of the laminate is topped with a self-adhering decorative layer prepared of porous polyester. For shipping and storage a second peeling layer prepared from any standard release paper which is impermeable to the therapeutic agent is placed over the outer layer.

30 The final camphor controlled release device is a laminate cut into pieces of 0.5 cm x 2 cm and about 300 microns thick. The device is safely and conveniently used by peeling the release paper from each face of the

laminate and pressing against the skin above a user's upper lip. Camphor will be released in a controlled manner for a period of about 12 hours.

5 Having thus described preferred exemplary embodiments of the present invention, it should be noted by those skilled in the art that the disclosures herein are exemplary only and that alternatives, adaptations and modifications may be made within the scope of the present invention.

CLAIMS

1. A device useful for the controlled release of one or more active compound said device forming a laminate comprising:
 - a diffusion rate limiting membrane layer;
 - 5 a reservoir layer adjacent said diffusion rate limiting membrane layer, said reservoir layer incorporating said active compound;
 - a vapor and liquid impermeable backing layer adjacent said reservoir layer; and
 - 10 an outer surface pressure sensitive adhesive layer adjacent said impermeable backing layer.
2. The device of Claim 1 further comprising a decorative layer adjacent said diffusion rate limiting membrane layer.
3. The device of Claim 1 wherein said adhesive layer comprises a biocompatible, hypoallergenic pressure sensitive adhesive.
4. The device of Claim 1 wherein said active compound is selected from the group of vapor emitting compounds or aerosols or aerosols consisting of perfumes, fragrances, essential oil fragrances,
5 insecticides, air fresheners, breath fresheners, therapeutic agents and insect repellents.
5. The device of Claim 1 wherein said vapor and liquid impermeable layer is a metal foil polymer laminate, said polymer selected from the group consisting of polyethylene terephthalate, high density
5 polyethylene, low density polyethylene, polypropylene, polyvinylchloride, and ethylene vinyl acetate, and polyester.

6. The device of Claim 1 wherein said reservoir layer comprises a porous polymer, said polymer having pores sized from about 0.02 microns to about 0.6 microns and porosity of 0.1 to about 0.8, and said active
5 compound incorporated within said pores.

7. The device of Claim 1 wherein said reservoir layer comprises a polymer and said active compound is dissolved in said polymer.

8. The device of Claim 1 wherein said reservoir layer comprises a gelled mixture of a polymer, a liquid, and said active compound.

9. The device of Claim 1 wherein said diffusion rate limiting membrane is a non-porous polymeric membrane, or a microporous polymer having a pore size of from about 0.02 microns to about 0.6 microns, said
5 polymer selected from the group consisting of polyethylene, polypropylene, polyvinylchloride, cellulose acetate, cellulose nitrate, polyacrylonitrile, polytetrafluoroethylene, and ethylene vinyl acetate.

10. The device of Claim 1 further comprising one or more clips extending from adjacent said diffusion rate limiting membrane to adjacent said impermeable backing.

11. The device of Claim 1 further comprising laminate layer edges secured by a sealing technique selected from the group consisting of solvent sealing and heat sealing.

12. A device useful for the controlled release of therapeutic agents, said device forming a laminate comprising:

a diffusion rate limiting membrane comprising
5 a polymer selected from the group consisting of nonporous polymeric membranes and microporous polymeric membranes having a pore size of from about 0.02 microns to about 0.6 microns;

a reservoir layer adjacent said diffusion rate
10 limiting membrane layer, said reservoir layer comprising one or more therapeutic agents incorporated in a polymer, said therapeutic agent selected from the group of vapor emitting compounds or aerosols consisting of antihistamines, bronchodilators, decongestants,
15 mucolytics, anti-tussives, anti-inflammatory steroids, anti-viral, peptides and hormones;

a vapor and liquid impermeable backing layer adjacent said reservoir layer; and

a pressure sensitive contact adhesive layer
20 adjacent said vapor and liquid impermeable backing layer, said adhesive layer comprising a biocompatible, hypoallergenic pressure sensitive adhesive.

13. The device of Claim 12 wherein said polymer is selected from the group consisting of polyethylene, polypropylene, polyvinylchloride, cellulose acetate, cellulose nitrate, polyacrylonitrile,
5 polytetrafluorethylene, and ethylenevinyl acetate.

14. The device of Claim 12 wherein said vapor and liquid impermeable backing layer is a metal foil polymer laminate, said polymer selected from the group consisting of polyethylene terephthalate, high density
5 polyethylene, low density polyethylene, polypropylene, polyvinylchloride, and ethylene vinyl acetate, and polyester.

15. The device of Claim 12 wherein said reservoir layer comprises a porous polymer, said polymer having pores sized from about 0.02 microns to about 0.6

microns, and said therapeutic agent incorporated within
5 said pores.

16. The device of Claim 12 wherein said reservoir layer comprises a polymer and said active compound is dissolved in said polymer or the polymer is polymerized in the presence of active compound.

17. The device of Claim 12 wherein said reservoir layer comprises a gelled mixture of a polymer, a liquid, and said therapeutic agent.

18. The device of Claim 12 further including an outer decorative layer adjacent said diffusion rate limiting membrane layer.

19. The device of Claim 12 further including laminate layer edges secured by a sealing technique selected from the group consisting of solvent sealing and heat sealing.

20. A device useful for the controlled release of insect repellent, said device forming a laminate comprising:

a diffusion rate limiting membrane comprising
5 a polymer selected from the group consisting of nonporous polymeric membranes and microporous polymeric membranes having a pore size of from about 0.02 microns to about 0.6 microns;

a reservoir layer adjacent said diffusion rate
10 limiting membrane layer, said reservoir layer comprising an insect repellent incorporated in a polymer;

a vapor and liquid impermeable backing layer adjacent said reservoir layer; and

a pressure sensitive contact adhesive layer
15 adjacent said vapor and liquid impermeable backing

layer, said adhesive layer comprising a biocompatible, hypoallergenic pressure sensitive adhesive.

21. The device of Claim 20 wherein said polymer is selected from the group consisting of polyethylene, polypropylene, polyvinylchloride, cellulose acetate, cellulose nitrate, polyacrylonitrile,
5 polytetrafluorethylene, and ethylenevinyl acetate.

22. The device of Claim 20 wherein said vapor and liquid impermeable backing layer is a metal foil polymer laminate, said polymer selected from the group consisting of polyethylene terephthalate, high density
5 polyethylene, low density polyethylene, polypropylene, polyvinylchloride, and ethylene vinyl acetate, and polyester.

23. The device of Claim 20 wherein said reservoir layer comprises a porous polymer, said polymer having pores sized from about 0.02 microns to about 0.6 microns, and said therapeutic agent incorporated within
5 said pores.

24. The device of Claim 20 wherein said reservoir layer comprises a polymer and said active compound is dissolved in said polymer, or the polymer is polymerized in the presence of active compound.

25. The device of Claim 20 wherein said reservoir layer comprises a gelled mixture of a polymer, a liquid, and said insect-repellent.

26. The device of Claim 20 further including an outer decorative layer adjacent said diffusion rate limiting membrane layer.

27. The device of Claim 20 further including laminate layer edges secured by a sealing technique selected from the group consisting of solvent sealing and heat sealing.

28. A method for the controlled delivery of therapeutic agents to the nasal cavity and respiratory airway of a patient, said method comprising the steps of:

- 5 providing a controlled delivery device, said device forming a laminate comprising:
- a diffusion rate limiting membrane layer;
 - a reservoir layer adjacent said diffusion rate limiting membrane layer, said reservoir layer
 - 10 incorporating one or more therapeutic agents;
 - a vapor and liquid impermeable backing layer adjacent said reservoir layer; and
 - a pressure sensitive adhesive layer adjacent said impermeable backing layer; and
 - 15 adhering said controlled delivery device to the skin in proximity of the nose.

29. The method of claim 28 wherein said therapeutic agent is selected from the group of vapor emitting compounds or aerosols consisting of antihistamines, bronchodilators, decongestants, mucolytics,

5 anti-inflammatory steroids, anti-tussives, anti-viral, peptides and hormones.

30. A method for the controlled delivery of insect repellent, said method comprising the steps of:

- providing a controlled delivery device, said device forming a laminate comprising:
- 5 a diffusion rate limiting membrane layer;
- a reservoir layer adjacent said diffusion rate limiting membrane layer, said reservoir layer incorporating one or more insect repellents;

a vapor and liquid impermeable backing
10 layer adjacent said reservoir layer; and
a pressure sensitive adhesive layer
adjacent said impermeable backing layer; and
adhering said controlled delivery device to
different parts of the skin or clothes of said user.

31. The method of claim 30 wherein said insect
repellent is N,N-diethyl-meta-toluamide.

Fig. 1.

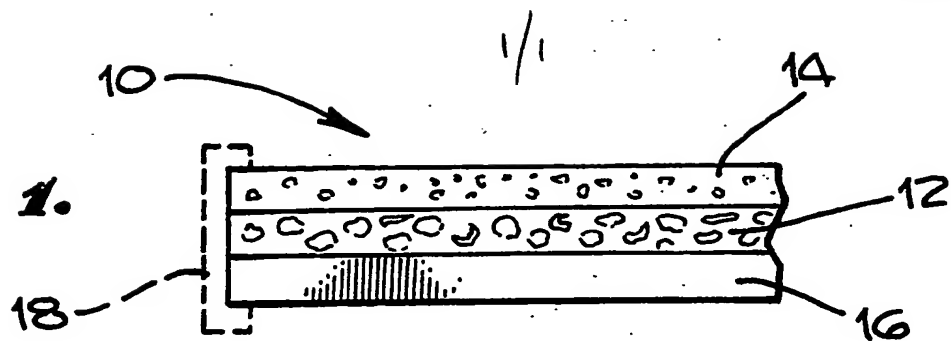


Fig. 2.

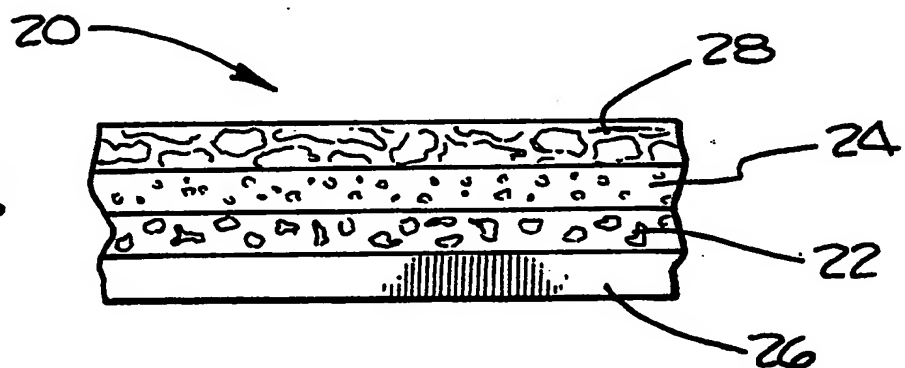


Fig. 3.

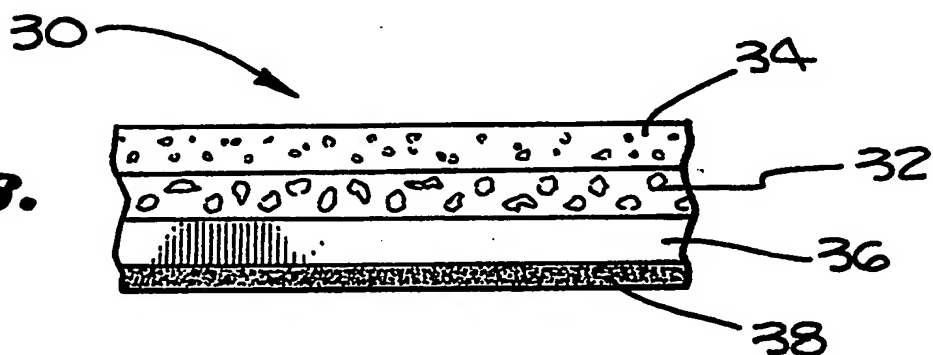
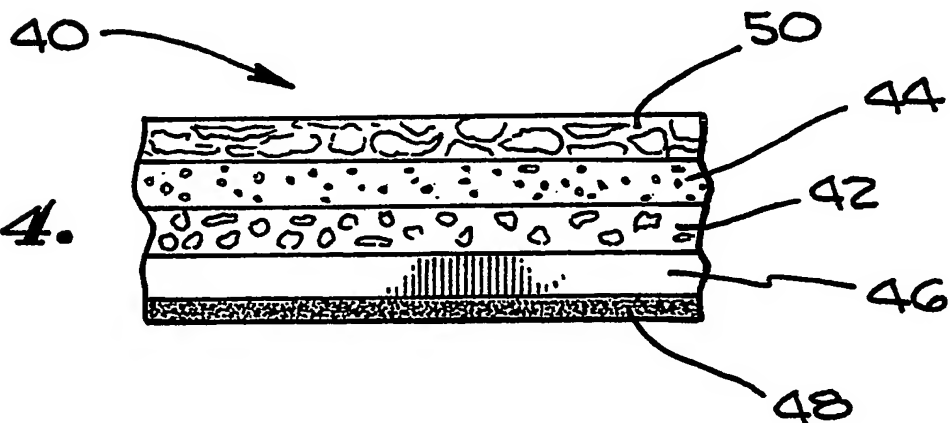


Fig. 4.



INTERNATIONAL SEARCH REPORT

International application No.

CT/US92/05452

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61L 9/04

US CL :239/6,36; 424/448, 449; 428/343, 354, 905

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : NONE

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| X Y | US,A 4,874,129 (DiSapio) 17 October 1989 see entire document. | 1-11 12-31 |
| Y | US,A, 4,445,641 (Baker) 01 May 1984 see entire document. | 1-31 |

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

| | | | |
|-------|---|-----|--|
| * "A" | Special categories of cited documents: document defining the general state of the art which is not considered to be part of particular relevance | "T" | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| "E" | earlier document published on or after the international filing date | "X" | document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| "L" | document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | "Y" | document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| "O" | document referring to an oral disclosure, use, exhibition or other means | "Z" | document member of the same patent family |
| "P" | document published prior to the international filing date but later than the priority date claimed | | |

Date of the actual completion of the international search

11 AUGUST 1992

Date of mailing of the international search report

28 OCT 1992

Name and mailing address of the ISA/
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Authorized officer

CHRISTOPHER BROWN

Facsimile No. NOT APPLICABLE

Telephone No. (703) 308-2351

Form PCT/ISA/210 (second sheet)(July 1992)*